EXHIBIT C

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

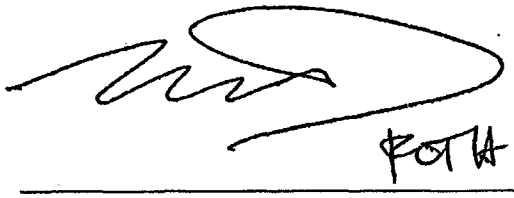
IN RE: ETHICON, INC. **PELVIC REPAIR SYSTEM** **PRODUCTS LIABILITY LITIGATION**	**Master File No. 2:12-MD-02327** **MDL No. 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

DEFENSE EXPERT GENERAL REPORT

of Ted Roth, M.D.

Prolift, Prolift+M and Gynemesh PS

Prepared by:



Ted Roth, M.D.

January 31, 2017

I. Qualifications and Experience

I am Board certified in Obstetrics & Gynecology with subspecialty Board certification in Female Pelvic Medicine and Reconstructive Surgery. After attending Johns Hopkins University as an undergraduate, I attended medical school at the University of Rochester and completed my residency in Obstetrics & Gynecology at Duke University under Charles Hammond. As a graduating chief resident, I received awards for outstanding surgical technique and outstanding laparoscopic skills. I continued my subspecialty training in Reconstructive Pelvic Surgery at the University of Mississippi Medical Center under G. Rodney Meeks.

I am currently the Chief of Gynecology and Medical Director of the Bladder Control Center of Central Maine Medical Center. I have implanted approximately 160 Prolifts and 80 Prolift+Ms, as well as other transvaginal mesh kits. Before Prolift was launched I used tailored Gynemesh PS to augment anterior repairs. I have performed hundreds of abdominal sacrocolpopexies, and in approximately 200 of those I used Gynemesh PS. I also have extensive experience in managing mesh complications that are referred to me by other surgeons and primary care providers.

I have presented numerous abstracts at medical society meetings and published numerous articles in peer-reviewed medical journals as well as book chapters on reconstructive gynecologic surgery. I serve as a reviewer for peer-reviewed medical journals including the International Urogynecology Journal, Female Pelvic Medicine and Reconstructive Surgery, Journal of Urology, and European Journal of Obstetrics & Gynecology and Reproductive Biology.

I have taught professional education courses and led cadaver labs on both SUI and POP products for Ethicon and have been on the speaker's bureau of Pfizer, GSK, Allergan, and Shionogi. I have also led professional education events for and served as a consultant for Medtronic.

My *curriculum vitae* is attached.

II. Materials Reviewed

My opinions set forth in this report are based on my clinical and surgical experience in both academic and community practice; my research and teaching; my analysis of the medical literature concerning the efficacy and safety of transvaginal mesh including Prolift, Prolift+M and Gynemesh PS; my analysis of the Prolift, Prolift+M and Gynemesh PS Instructions for Use; and my review of professional education materials for users of the products, including the Prolift Surgeons' Resource Monograph, Prolift Surgical Technique Guide, PowerPoint presentations, surgical videos and anatomy animations, as well as the patient brochures; my participation in professional medical societies; review of medical society statements; discussions with peers at conferences and other professional events in my field; and my education and training. My opinions are also based on my review of deposition testimony and exhibits, expert reports and the materials they cite to, and other materials, including materials issued by the FDA. A complete list of the materials I have reviewed is attached to this report and will be supplemented as I review additional materials. My opinions and conclusions are based on the practice of

evidence-based medicine. All of my opinions set forth in this report are held to a reasonable degree of medical and scientific certainty and probability.

III. Fees and Testimonial History

My fees for serving as an expert in this matter are $600 per hour for report writing, review and consultation. For deposition or court testimony, my fee is $800 per hour. As of the writing of this report, I have not provided expert testimony in the Ethicon pelvic mesh litigation.

IV. Opinions

A. Introduction

Pelvic organ prolapse (POP) is a common condition and is defined as the descent of one or more pelvic organs, such as the bladder, uterus, vaginal vault, small bowel or rectum, into the vagina. Severity of prolapse is quantified through grading or staging according to the POP-Q system or the Baden-Walker system. (Persu C, et al, Pelvic organ prolapse quantification system (POP-Q) – a new era in pelvic prolapse staging, 2011, J Med Life 4(a):75-81.) POP is seen in 40 to 60% of parous women. (Maher CF et al., Surgical management of pelvic organ prolapse in women, Cochrane database syst rev. 2013, 4:CD004014.) A majority (70%) of women with POP have prolapse in more than one compartment of the vagina. (Olsen AL, et al, Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. 1997, Obstet Gynecol 89:501-505.) The lifetime risk of undergoing at least one surgical procedure to correct POP ranges from 6% to 19% (Olsen AL et al. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol 1997; 89(4): 501–6), (Smith FJ et al. Lifetime risk of undergoing surgery for pelvic organ prolapse. Obstet Gynecol 2010; 116(5): 1096–100). Approximately 1 out of 8 American women will undergo surgery for POP by age 80 (Wu JM et al. Lifetime risk of stress urinary incontinence or pelvic organ prolapse surgery. Obstet Gynecol 2014; 123:1201-6).

POP is a highly heterogeneous condition and the etiology is likely multi-factorial. Lifestyle factors (which are modifiable) such as obesity and smoking may contribute, as well as pregnancy and childbirth. There are variations in pelvic organ support within and between populations that are probably genetically determined (Dietz HP. Do Asian women have less pelvic organ mobility than Caucasians? International Urogynecol J Pelvic Floor Dysfunct 2003; 14:250–53). Genetic determinants of POP may be linked to collagen subtypes or connective tissue metabolism, but research has been inconclusive (Laborda E, Gelman W, Anthony F, Monga A. Is increased collagen metabolism the cause or effect of prolapse: a controlled study. Neurourol Urodynam 2003; 22:505–06), (Phillips CH, Anthony F, Benyon C, Monga AK. Collagen metabolism in the uterosacral ligaments and vaginal skin of women with uterine prolapse. BJOG 2006; 113:39–46).

Many reconstructive pelvic surgeons feel that prolapse is caused by distinctive fascial defects caused by vaginal childbirth (Richardson AC, Lyon JB, Williams NL. A new look at pelvic relaxation. Am J Obstet Gynecol 1976;126:568–73). The concept is appealing because of its simplicity, and it provides a clear rationale and task for the reconstructive surgeon; however, reliably identifying these defects may be challenging.

Some women with objective POP are asymptomatic and do not require treatment. Conversely, symptom bother may be considerable (Ulrich D, Guzman Rojas R, Dietz HP, Mann K, Trutnovsky G. Use of a visual analog scale for evaluation of bother from pelvic organ prolapse. Ultrasound Obstet Gynecol 2014;43:693–97). Pelvic organ prolapse can greatly affect a woman's quality of life, including social, psychological, occupational, domestic, physical, and sexual well-being (Lowder et al. Body image in women before and after reconstructive surgery for pelvic organ prolapse. Int Urogynecol J (2010) 21:919–925). Women with POP often have impaired quality of life (QOL) and are more likely to be self-conscious and suffer sexual dysfunction, and they are less likely to feel physically attractive than normal controls (Jelovsek JE, Barber MD. Women seeking treatment for advanced POP have decreased body image and quality of life. Am J Obstet Gynecol 2006; 194:1455-61). My own practice reflects what is documented in the medical literature, and I regularly see patients whose social and professional lives and their intimate relationships are moderately to severely affected by POP.

The most common symptoms associated with POP are those of a vaginal lump or bulge, vaginal pressure, or a 'dragging' sensation (Barber MD. Symptoms and outcome measures of pelvic organ prolapse. Clin Obstet Gynecol 2005; 48:648–61). At times, POP results in voiding dysfunction which can occur with urethral kinking (from a cystocele) or secondary to urethral compression by advanced uterovaginal prolapse, an enterocele, or a rectocele (Dietz HP, Haylen BT, Vancaillie TG. Female pelvic organ prolapse and voiding function. International Urogynecol J Pelvic Floor Dysfunct 2002;13:284–88). Posterior compartment prolapse (rectocele) may manifest with symptoms of obstructed defecation (Dietz H, Cartmill J. Imaging in patients with obstructed defecation. Tech Coloproctol 2013;17:473–74) which can require that women splint to effectuate bowel movements.

POP can also negatively impact sexual function. An increasing severity of sexual impairment has been associated with worsening prolapse, including dyspareunia, pelvic pain, fecal dysfunction and urinary dysfunction (Ellerkman et al. Correlation of symptoms with location and severity of pelvic organ prolapse. Am J Obstet Gynecol 2001 185 (6) 1332-1338). Older age and postmenopausal status, coexisting in women with POP, are also associated with impaired sexual dysfunction. Sexual function in women is multifactorial and is affected by psychological, social, and physical factors (Handa VL et al., Sexual function before and after sacrocolpopexy for pelvic organ prolapse, AJOG 2007 197: 629.e1-6). Studies evaluating sexual function in women with pelvic organ prolapse find baseline dyspareunia rates between 8-43%, making the

evaluation of de novo dyspareunia after surgical intervention difficult (Weber AM et al., Sexual function and vaginal anatomy in women before and after surgery for pelvic organ prolapse and urinary incontinence, AJOG 2000 182: 1610-5).

B. Non-Surgical Treatment of Pelvic Organ Prolapse

A non-surgical option for treating POP is use of a pessary, a removable device inserted into the vagina that provides support to the prolapsing organ(s). Pessaries require removal for cleaning and often for sexual intercourse, and many patients must return to the office for pessary cleaning multiple times a year. Complications of pessary use include vaginal discharge and odor, pain, fistula, erosion and subsequent impaction. (Jones, et al, Pessary use in pelvic organ prolapse and urinary incontinence 2010, Reviews in Obstetrics & Gynecology 3(1):3-9). A retrospective chart review found that more than half (56%) of pessary users had complications that lead to high discontinuation rates. (Sarma S, Ying T, Moore KH. Long-term vaginal ring pessary use: discontinuation rates and adverse events. BJOG. 2009;116(13):1715–1721.) Pelvic floor muscle training such as Kegel exercises is an option but has been demonstrated to have limited benefits for women who are already symptomatic with POP. (Wiegersma M et al, Effect of pelvic floor muscle training compared with watchful waiting in older women with symptomatic mild pelvic organ prolapse: randomized controlled trial in primary care. BMJ. 2014, 22:349; Braekken et al, Can pelvic floor muscle training reverse pelvic organ prolapse and reduce prolapse symptoms? An assessor-blinded, randomized, controlled trial. Am J Obstet Gynecol. 2010, 203(2):170.)

C. Surgical Treatment of Pelvic Organ Prolapse

The goals of surgery for POP are to restore anatomy, improve pelvic floor function, and to enhance quality of life. Choice of surgery namely, whether to perform a repair vaginally vs. abdominally, whether to perform augmentation with mesh vs. a native tissue repair, and which surgery to use--requires balancing considerations such as surgical outcomes and risks against other factors, such as differences in operating times (with longer operating times being associated with increased risk of blood loss, wound infection, deep venous thrombosis, pulmonary embolism and other serious complications), and differences in recovery time and return to activities of daily living, costs, and reoperation rates. These considerations need to be discussed and weighed by the patient and her surgeon when deciding on treatment of POP.

Patients with prolapse in multiple compartments typically require repairs to each symptomatic compartment (there is debate about whether asymptomatic compartments should be repaired). A challenge in treating POP is that patients with prolapse in one compartment may later develop prolapse in another compartment (or even recurrent prolapse in the original compartment).

i. Abdominal Sacral Colpopexy

Abdominal sacral colpopexy (ASC) with mesh (such as Gynemesh PS) can be performed as an open abdominal, laparoscopic or robotic procedure. An ASC repair involves the fixation of mesh to the vaginal apex and to the sacrum to repair vaginal vault prolapse. Gynemesh PS can be cut to the desired shape by the surgeon for use in ASC. The list of potential complications of ASC is the same as that of TVM. In a study of 215 ASC patients over a median of 7 years, Nygaard and colleagues found a rate of anatomic recurrence of 25%, an estimated probability of mesh exposure of 10.5% and a rate of surgical re-intervention after seven years of 16.7%. (Nygaard et al, Long-term outcomes following abdominal sacrocolpopexy for pelvic organ prolapse, JAMA, 2013, 310(10): 1076.) Minimally invasive robotic and laparoscopic approaches are associated with less morbidity than open ASC; however, robotic ASC involves longer operative times and greater expense, and laparoscopic ASC involves a longer learning curve for surgeons. (Gaines, et al., Pelvic Prolapse Repair in the Era of Mesh, Curr Urol Reports 2016, 17(20):1-9.)

ii. Native Tissue Repairs (NTRs)

Native tissue repair surgeries to treat prolapse, also called "traditional" repairs, include anterior colporrhaphy and paravaginal repair (anterior compartment), posterior colporrhaphy (posterior compartment) and sacrospinous ligament fixation and uterosacral ligament suspension (apical compartment). Most native tissue repairs are performed transvaginally.

I counsel my patients that after traditional surgery there is a high recurrence rate of 39% and a repeat rate of repair (for recurrence) of up to 29%, with cystocele, or anterior vaginal wall prolapse, being the most common kind of prolapse and the compartment most likely to fail. (Fialkow MF et al, Incidence of recurrent pelvic organ prolapse 10 years following primary surgical management: a retrospective cohort study, Int Urogyn, 2008 19:1483-7), (Olsen AL et al. Obstet Gynecol 1997; 89:501-6), (Whiteside et al. Risk factors for prolapse recurrence after vaginal repair. Am J Obset Gynecol 2004 191:1533-1538). The anatomic failure rates for native tissue repairs have been reported to range from 30% to 70% for the anterior vaginal wall and 20% for the posterior vaginal wall. (Milani et al., Outcomes and predictors of failure of trocar-guided vaginal mesh surgery for pelvic organ prolapse, Am J Obstet Gynecol (May 2012) 206:440.e1-8.)

Recent data suggest that the majority of POP recurrences are evident at the 1 year mark (Dietz HP, et al. The natural history of cystocele recurrence. Int Urogynecol J 2014 25 (8):1053-1057). Olsen and colleagues found in a retrospective cohort study of 395 women who underwent prolapse and incontinence repairs that not only did nearly 29.2% of the women subsequently undergo re-operation for urinary incontinence or POP, but that time intervals between procedures

decreased with each successive repair. (Olsen AL, et al, Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence, Obstet Gynecol 1997, 89(4): 501-506.)

Surgeons' ability to predict recurrence and the compartment in which the recurrence may be located remains quite limited. Levator ani avulsion has been specifically identified as being associated with a risk of recurrence after NTR (Dietz HP et al. Levator avulsion is a risk factor for cystocele recurrence. Ultrasound Obstet Gynecol 2010 36: 76-80).

iii. Rationale for Transvaginal Mesh (TVM) and the Design of the Prolift Kit

The advantage of a transvaginal repair using a mesh kit such as Prolift or Prolift+M is that it allows the surgeon to avoid the morbidity associated with entering the abdomen, and to perform surgery faster and with the flexibility to repair any compartment, along with a concomitant midurethral sling if indicated. (Gaines N et al, Pelvic prolapse repair in the era of mesh, Curr Urol Rep 2016, 17:20.)

Numerous studies have shown that transvaginal repair with mesh is superior to native tissue repair. The 2016 Cochrane Review analyzed 37 RCTs, 25 of which compared polypropylene TVM to NTRs Maher et al stated that low to moderate quality evidence suggested there are advantages to using transvaginal permanent mesh compared to native tissue repair, including lower rates of awareness of prolapse, reoperation for prolapse, and recurrent prolapse on examination; that if 19% of women are aware of prolapse after native tissue repair, between 10% and 15% will be aware of prolapse after permanent mesh repair, and if the rate of recurrent prolapse on examination after a native tissue repair is assumed to be 38%, the risk would be between 11% and 20% after a repair with transvaginal permanent mesh. (Maher CF et al, Transvaginal mesh or grafts compared with native tissue repair for vaginal prolapse, Cochrane database syst rev 2016.)

The transvaginal use of Gynemesh PS and the development of Prolift, a transvaginal mesh (TVM) kit, met a need to improve anatomic cure rates of native tissue repair, maintain a minimally invasive platform, and reduce morbidity associated with abdominal procedures.

The idea for transvaginal mesh (TVM) procedures was predicated on evidence from 1) the hernia literature which documented improved cure rates when herniorrhaphy was performed with the addition of a synthetic graft; (ACOG Committee Opinion no. 513: vaginal placement of synthetic mesh for pelvic organ prolapse. Obstet Gynecol 2011;118(6):1459–64) and 2) Long-term safety and outcomes from transvaginally placed mesh for SUI. As surgeons, however, we realize that the functional requirements of vaginal repairs differ drastically from abdominal hernia repair; the need for optimal urinary, defecatory, and sexual function requires that a repair be more than just durable.

In TVM kit procedures, synthetic polypropylene mesh is inserted transvaginally into the vesicovaginal and/or rectovaginal space, with the sacrospinous ligaments (SSL) usually being used as an apical fixation point. With Prolift, Gynemesh PS (a nonabsorbable, type I, macroporous, monofilament polypropylene mesh) is inserted through a full thickness vaginal incision to place the mesh in the vesicovaginal / rectovaginal space. The Prolift trocars are used by the surgeon to place the pre-cut mesh; the surgeon uses palpation, proprioception, and his or her 3-D knowledge of pelvic floor anatomy to pass the trocars through the arcus tendinous fasciae pelvis (ATFP) or the SSL. Retrieval loops acquire the mesh arms through the trocars. Although Plaintiffs' experts have criticized the "blind passage" of the guides, blind passage techniques are not unique to Prolift and are used in laparoscopy and in non-mesh prolapse repair procedures. *The skill set and the anatomical knowledge used for Prolift are no different than for other procedures performed by reconstructive pelvic surgeons.*

Prolift was developed by surgeons experienced in the use of synthetic material for prolapse repairs who sought to standardize a minimally invasive technique for the surgical management of prolapse via the vaginal approach using low-weight and high-porosity Gynemesh PS, which had been clinically shown to be both safe and efficacious. (Berrocal, et al, Conceptual advances in the surgical management of genital prolapse: The TVM technique emergence, J Gynecol Obstet Biol Reprod 2004, 33:577-587; Lucente, et al, A clinical assessment of Gynemesh PS for the repair of pelvic organ prolapse, AUGS – SGS Oral Poster 55) With guides, cannulas and retrieval devices that allow for minimally invasive placement of the mesh via a transvaginal approach, the design of the Prolift kit met those needs.

iv. Evidence from RCTs

Numerous RCTs have provided level one evidence of the safety and efficacy of Gynemesh PS and Prolift as compared to native tissue repair. My results with Prolift are consistent with the results reported in the literature.

Withagen's multicenter (13 centers/22 surgeons) RCT compared Prolift with conventional vaginal repair in 190 women with *recurrent POP* (many of whom had failed an ASC). The study demonstrated superiority of Prolift over nonmesh repairs for both anterior and posterior compartments. At 12 months in the posterior wall there was 4.1% failure in the mesh vs. 24.5% in the nonmesh group (P= .003). In the anterior wall there was 7.8% failure in the mesh vs. 55.1% in the nonmesh group (P <.001). 14 of 83 patients, or 16.9%, in the Prolift group had mesh exposure, although 9 of those 14 were asymptomatic. 9 patients were treated with topical estrogen cream only and 5 had excision as outpatients. Rates of other complications, including postoperative pain and dyspareunia, are low and comparable in both groups (Withagen MI et al. Trocar guided mesh compared with conventional vaginal repair in recurrent prolapse: a RCT. Obstet Gynecol 2011 117(2): 242-50).

Svabik et al, compared Prolift to NTR with sacrospinous ligament fixation in a RCT of 70 patients with post-hysterectomy (apical) prolapse and levator avulsion. At 1 year they observed only 1 case of anatomic failure in the Prolift group (3%) and 22 cases in the SSL group (65%) (P <.001); the higher anatomical success rate in the Prolift group was further demonstrated in significant differences between the Prolift and SSF groups for all POP-Q parameters except genital hiatal diameter, perineal body length and total vaginal length. Rate of de novo dyspareunia was not different between the two groups (Svabik K , et al., Comparison of vaginal mesh repair with sacrospinous vaginal colpopexy in the management of vaginal vault prolapse after hysterectomy in patients with levator ani avulsion: a randomized controlled trial, Ultrasound Obstet Gynecol 2014;43 :365-371).

In a RCT that compared SSL fixation to Prolift for apical prolapse in 168 patients, Halaska et al, found POP recurrence at 12 months occurred in 39.4% of the SSF group and in 16.9% of the mesh group (P=.003). There was no detectable difference in QOL measures and no statistically significant difference in pelvic pain between the two patient groups. There also was no significant difference in changes in quality of sexual life between the SSF and Prolift groups. Mesh exposure was seen in 20.8% of patients at one year, only one-quarter of whom were symptomatic, and all exposures were successfully treated with topical estrogen therapy, excision under local anesthesia or excision under general anesthesia (Halaska M et al., A multicenter, randomized, prospective, controlled study comparing sacrospinous fixation and transvaginal mesh in the treatment of posthysterectomy vaginal vault prolapse, AJOG 2012 207: 301.e1-7).

Altman et al showed that Prolift was superior to native tissue (anterior colporrhaphy) in anatomic and subjective cure at 1 year with composite success rates of 60.8% in the TVM compared with 34.5% in the native tissue group (95% confidence interval [CI] 15.6–37.0). The main treatment effect of Prolift was observed at 2 months and 12 months and persisted even after imputation of missing data to the disadvantage of Prolift. The rate of serious surgical complications attributed to Prolift was 4% and was similar to the rates seen in other multicenter studies; surgery to address mesh complications was reported in 3% of the women receiving a Prolift repair (Altman D et al., Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse, N Engl J Med. 2011; 364: 1826-36).

a. TVM for Anterior Wall Prolapse

Most currently available literature on transvaginal mesh in POP repair evaluates its use in the anterior vaginal compartment - the most common site of prolapse. Over 80 percent of surgical POP repairs involve the anterior vaginal wall. (Olsen AL, et al, Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence, Obstet Gynecol, 1997, 89:501-505.)

The superiority of TVM in treating anterior wall prolapse, compared with NTR, has been demonstrated in numerous RCTs. The 2016 Cochrane Review included 17 RCTs comparing native tissue repair with permanent mesh in the anterior wall, and found that the benefit in the mesh group was more pronounced than when the analysis included repairs in all compartment, and statistical heterogeneity was much reduced (RR 0.33, 95% CI 0.26 to 0.40, 15 RCTs, n = 1748, I2 = 10%). (Maher CF et al, Transvaginal mesh or grafts compared with native tissue repair for vaginal prolapse, Cochrane database syst rev 2016.) Schimpf's 2016 meta-analysis concluded that in the anterior vaginal compartment, synthetic nonabsorbable mesh consistently showed improved anatomic outcomes and bulge symptoms compared with native tissue repairs. (Schimpf, MO et al, Graft and Mesh Use in Transvaginal Prolapse Repair, A Systematic Review, Obstet Gynecol 2016, 128(10:81-91.)

The Altman RCT, discussed above, was one of the largest RCTs comparing native tissue anterior repair with Prolift. As noted above, Altman et al showed that Prolift was superior to native tissue in anatomic and subjective cure at 1 year with composite success rates of 60.8% in the Prolift group compared with 34.5% in the native tissue group (95% confidence interval [CI] 15.6–37.0).

DaSilveira's multicenter RCT, which assessed 184 women with prolapse of stage 3 or 4 assigned to either Prolift or SSLF, demonstrated superior anatomical efficacy for the anterior compartment and superior quality of life measures in the Prolift group. (Da Silveira, et al, Multicenter, randomized trial comparing native vaginal tissue repair and synthetic mesh repair for genital prolapse surgical treatment, Int Urogynecol J 2014, DOI 10.1007/s00192-014-2501-z.)

b. TVM for Apical Prolapse

Defects in the anterior and apical compartments frequently coexist. (Rooney K, et al, Advanced anterior vaginal wall prolapse is highly correlated with apical prolapse, Am J Obstet Gynecol, 2006, 195(6):1837-1840.) The efficacy of TVM in treating apical prolapse has also been demonstrated in the scientific literature. As noted above, Halaska's 2012 RCT found POP recurrence at 12 months occurred in 39.4% of the SSLF group and in 16.9% of the mesh group (P=.003) (Halaska 2012). Svabik's RCT, also discussed above, found higher anatomical success rate in the Prolift group and only 1 case of anatomic failure in the Prolift group (3%) vs 22 cases in the SSL group. (Svabik 2014.)

Feiner et al (2009) conducted a systematic review of mesh kits for apical defects. Overall, posterior or total Prolift (both which provide apical support) was performed in 1,295 women with a mean follow-up of 30 weeks (12-52 weeks). The mean objective success rate was 87% (75-94) and mean complication rate was 16% (2-61). (There were inconsistencies for what defined success secondary to use of varied grading systems for POP quantification.) In the Prolift group, the rate of mesh exposure was 7% and the rate of dyspareunia was 2%. The

authors concluded that Prolift was effective in restoring apical support (Feiner B et al., Efficacy and safety of transvaginal mesh kits in the treatment of prolapse of the vaginal apex: a systematic review, BJOG 2009 116: 15-24).

c. TVM for Posterior Wall Prolapse

As discussed above, Withagen's RCT compared Prolift with conventional vaginal repair in women with recurrent POP. That study demonstrated superiority of mesh over nonmesh repair for the posterior compartment as well as the anterior compartment. At 12 months, in the posterior wall, there was 4.1% failure in the mesh vs. 24.5% in the nonmesh group (P= .003). (Withagen MI et al. Trocar guided mesh compared with conventional vaginal repair in recurrent prolapse: a RCT. Obstet Gynecol 2011 117(2): 242-50).

Sand and Paraiso have shown a similar rectocele recurrence rate both with and without the use of graft reinforcement but neither assessed Gynemesh PS or Prolift. (Sand et al, Prospective randomized trial of polyglactin 910 mesh to prevent recurrence of cystoceles and rectoceles, Am J Obstet Gynecol June 2011, 1357-1364)(the mesh used was Vicryl mesh, not Gynemesh PS); (Paraiso et al, Rectocele repair: A randomized trial of three surgical techniques including graft augmentation, Am J Obstet Gynecol 2006, 195:1762-1771) (mesh used was a porcine-derived mesh not Gynemesh PS).

d. Quality of Life (QOL) and Patient-Centered Outcomes

Prolift has also been demonstrated to improve quality of life and subjective outcomes from prolapse repair.

Patient-centered outcomes research for POP suggests that anatomic outcomes/success may not always correlate with patients' perception of success after prolapse surgery, and that the absence of a sensation of vaginal bulge (i.e. symptomatic relief), rather than strict criteria of anatomic success alone, impacts overall patient perception of improvement.

Most of the early studies of TVM were not designed to detect differences in subjective outcomes, however Altman's RCT used a composite outcome of both anatomic and symptomatic results. The symptom of vaginal bulge between groups was not different at 2 months, but at 1 year, 37.9% of the NTR group vs. only 24.6% of the TVM felt symptomatic bulging (P=.008).

In Da Silveira's RCT (NTR vs Prolift) which showed better anatomical cure rates in the mesh group, between-group comparisons also revealed greater improvement in QOL in the mesh group.

Balchandra et al. analyzed preoperative and postoperative validated questionnaires completed by 51 women who underwent repair with a TVM kit. There were statistically significant improvements in "dragging pain," "vaginal soreness," "reduced vaginal sensation," "vaginal laxity," "lump in the vagina," "vaginal dryness," and "splinting of the vagina." Average QOL scores were statistically improved ($p < .05$) (Balchandra P et al. Perioperative outcomes and prospective patient reported outcome measures for transvaginal mesh surgery. Arch Gynecol Obstet 2015 DOI 10.1007/s00404-015-3724-z).

v. Complications

The risks of transvaginal mesh, transvaginal mesh kits, ASC with mesh *and* non-mesh repairs for POP include the following, all of which are commonly known to experienced pelvic surgeons:

- Acute and/or chronic pain with intercourse
- Acute and/or chronic pain
- Vaginal scarring
- Infection
- Urinary problems, including urinary frequency, urgency, dysuria, retention or obstruction, incontinence
- Organ or nerve damage
- Bleeding
- Wound complications
- Inflammation
- Fistula formation
- Neuromuscular problems in pelvic floor muscles, lower extremities and/or abdominal area
- One or more surgeries to treat an adverse event
- Recurrence or failure
- Foreign body response
- Erosion/exposure/extrusion of mesh

Critics of the use of mesh state that it introduces risks not present in traditional non-mesh surgery for POP repair. However, the risks for patients undergoing a repair using mesh comprise the same risks faced by patients undergoing non-mesh procedures.

For example, in Barber's RCT of 374 women undergoing sacrospinous ligament fixation vs. uterosacral ligament suspension, 16% of patients in both groups experienced serious adverse events, including neuropathic pain (12% in SSLF group and 7% in USLS group). Karram and colleagues' study of posterior compartment repairs found a de novo dyspareunia rate of 18%.

(Karram et al, Surgery for posterior vaginal wall prolapse, Int Urogynecol J 2013, 24:1835-1841.) And Dietz and colleagues found a 48% rate of prolapse recurrence (defined as POP-Q stage 2 or above) in their retrospective review of 166 patients who had anterior colporrhaphy. The 2016 Cochrane Review by Maher and colleagues found no difference between the TVM and NTR groups with respect to the complications of de novo bladder overactivity and de novo dyspareunia.

Mesh exposure is a risk of transvaginal mesh, including Prolift, Prolift+M and Gynemesh PS, and yet it is also a risk of other prolapse repair surgeries (including ASC, sacrospinous ligament fixation, uterosacral suspension, and paravaginal repair, as well as transvaginal repairs using other types of grafts) that rely on a synthetic mesh, a xenograft or allograft, or permanent sutures. All of these are associated with a risk of exposure and pain, sometimes requiring removal. The rate of mesh exposure found by Maher and colleagues in the 2016 Cochrane Review was 12%, although only 8% required surgical intervention for mesh exposure. This rate is consistent with the rate that I see in my own practice.

In a well-known large RCT of women undergoing ASC, the mesh exposure rate at 12 months was 4.3% (the number requiring intervention was not noted) (Brubaker L et al., Two-year outcomes after sacrocolpopexy with and without Burch to prevent stress urinary incontinence, Obstet Gynecol 2008 112(1): 49-55). Barber et al noted a 15.4% suture exposure rate after uterosacral suspension and 17.2% suture exposure rate after sacrospinous fixation) (Barber MD et al., Comparison of 2 transvaginal surgical approaches and perioperative behavioral therapy for apical vaginal prolapse: the OPTIMAL randomized trial, JAMA 2014; 311(10):1023-34). Permanent suture use during posterior repair was studied retrospectively by Luck and colleagues who found that suture erosion/wound dehiscence occurred in 31% in the permanent suture group vs. 9 in the absorbable suture group (P=.003), and the need for additional surgical intervention was 16% in the permanent suture group vs. none in the absorbable suture group (Luck AM et al. Suture erosion and wound dehiscence with permanent versus absorbable suture in reconstructive posterior vaginal surgery. AJOG 2005 192: 1626-9).

Although the 2011 FDA "Update on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse" suggested "that in most cases, POP can be treated successfully without mesh thus avoiding the risk of mesh-related complications," traditional repairs are associated with the same set of complications as mesh-augmented repairs, as described above. While mesh exposure is a complication that is unique to repairs using mesh, the risk of mesh exposure can be weighed by the patient and her surgeon against risks associated with traditional repairs, including a higher rate of recurrence as previously elaborated in this report. Moreover, many mesh exposures are either asymptomatic or can be managed conservatively.

While the FDA Safety Communication noted that patients should be counseled about TVM and the "potential for serious complications and their effect on quality of life, including pain during intercourse," surgeons should counsel their patients about the potential complications of prolapse repair regardless of whether mesh is used or not. As noted above, pain during intercourse is a potential complication of any prolapse repair and any vaginal surgery. Although complications of TVM can go unreported to the MAUDE database (Deng et al, has commented on the nature of under-reporting of complications in the MAUDE database vs. the literature (Deng D et al., Presentation and management of major complications of midurethral slings: Are complications under-reported? Neurourol Urodyn 2007;26:46–52)), for native tissue repairs, no FDA-monitored device is utilized and thus they remain untracked by any comparable reporting mechanism.

vi. Surgical Volume and TVM Complications

Studies have demonstrated that surgeon experience and volume has a positive association on TVM-associated complications and exposure (Barski D, Otto T, Gerullis H. Systematic review and classification of complications after anterior, posterior, apical, and total vaginal mesh implantation for prolapse repair. Surg Technol Int 2014; 24: 217-24) (Deng T, et al. Risk factors for mesh erosion after female pelvic floor reconstructive surgery: a systematic review and meta-analysis, BJU Int 2016; 117: 323-43). There remains uncertainty about the estimating the absolute risk of a particular complication attributable to surgeon volume.

This phenomenon is not unique for TVM surgeries, of course. Several studies have demonstrated a relationship between higher provider volumes and improved outcomes for other surgical procedures such as coronary artery bypass grafting, aortic aneurysm repair, carotid endarterectomy, complex gastrointestinal surgeries and gynecologic surgeries (Luft HS, Hunt SS, Maerki SC. The volume-outcome relationship: practice-makes-perfect or selective-referral patterns? Health Serv Res. 1987, 22: 157-182) (Mowat A et al. Surgical outcomes for low-volume vs high-volume surgeons in gynecology surgery: a systematic review and meta-analysis. AJOG 2016 July: 21-33).

Kelly et al found an inverse relationship between surgeon procedural volume and complications in TVM; patients of very high volume surgeons had a 41% reduction in the risk of mesh complications and reoperation (Kelly EC, et al. Surgeon experience and complications of transvaginal prolapse mesh, Obstet Gynecol 2016; 127). In addition, these authors identified four risk factors for mesh complications: younger patient age, concurrent hysterectomy, blood transfusion, and increased patient comorbidity (their report was however limited by data sources and what covariates they could study). Ultimately, their cumulative incidence rate of mesh complication requiring surgery was 5.15% at 10 years. This is consistent with Jonsson Funk's

report citing a 5.9% 5-year risk of mesh revision or removal for mesh related complications (Jonsson Funk M et al. Long-term outcomes of vaginal mesh vs native tissue repair for anterior vaginal wall prolapse. Int Urogynecol J 2013;24: 1279-85).

vii. What Are Risk Factors for Mesh-Based Complications ?

Withagen et al conducted a prospective cohort study on 294 women undergoing Prolift and logistic regression analysis was performed to identify risk factors for exposure, dyspareunia and pain. Smoking, total mesh use, and experience (years of experience in doing POP repair) were predictive factors for mesh exposure. Pain and dyspareunia preoperatively were predictive for pain and dyspareunia postop (Withagen MI et al. Obstet Gynecol 2011 118(3) 629-636). It is common knowledge to surgeons that smoking is a risk for poor wound healing in any surgery. Not dissimilar, risk factors for mesh exposure after anterior Prolift were found to be smoking and rheumatologic diseases (Elmer C. et al. Neurourol Uro 2012 DOI 10.1002/nau).

a. Exposure

With Prolift, mesh exposure typically occurs along the incision line. The etiology is multi-factorial: technique of wound closure, hematoma formation, and failure to identify the proper surgical plane. Mesh exposure may be asymptomatic, and the majority of mesh exposures can be treated conservatively (with application of estrogen cream). (Skoczylas, et al, Managing mesh exposure following vaginal prolapse repair: a decision analysis comparing conservative versus surgical treatment, Int Urogynecol J, 2013, 24:119-125.) Some mesh exposures require in-office trimming and others may require mesh excision in the OR.

In Lowman et al (Lowman et al. Does the Prolift system cause dyspareunia? AJOG 2008 199:707.e1-707.e6), 8 of 21 women with mesh exposure were sexually active, but only 2 reported dyspareunia; thus, mesh exposure was not associated with dyspareunia.

The reoperation rate for mesh-related complications in a cohort of 524 Prolift patients (with a mean follow-up of 38 months) was 3.6% (2.5% mesh exposure, 0.2% mesh infection, and 0.4% for mesh retraction) (de Landsheere L, et al., Surgical intervention after transvaginal Prolift mesh repair: retrospective single-center study including 524 patients with 3 years' median follow-up, Am J Obstet Gynecol. 2012 Jan; 206(1):83.e1-7. DOI: 10.1016/j.ajog.2011.07.040). Prolapse recurrence in the compartment receiving mesh was 3%.

Rates of mesh exposure after Prolift, in general, for all compartments implanted, range from 0 - 15% with follow-up ranging from 12 months to 10 years. In comparison, reported rates of mesh exposure for sacrocolpopexy are between 6 - 9% (Ross JW et al., Laparoscopic sacrocolpopexy for severe vaginal vault prolapse: five-year outcome, J Min Inv Gynecol 2005 12: 221-6) (Higgs PJ et al., Long term review of laparoscopic sacrocolpopexy, BJOG 2005 112:1134-8). In the

CARE study involving sacrocolpopexy (Nygaard I, et al., Long-term Outcomes Following Abdominal Sacrocolpopexy for Pelvic Organ Prolapse, JAMA 2013, 309(19):2016-2024), 23 of 90 women (representing 39% of the original cohort being available at 7 years) had mesh exposures – 13 had mesh removed via a vaginal approach, 2 via an abdominal route, 4 were treated with topical estrogen, and 4 were asymptomatic).

Overall severity of complications associated with ASC (not just mesh-related) can be more significant than those associated with TVM kits including Prolift. ASC/laparoscopic SCP involves risks that are not attendant to TVM kits, including incisional hernia, bowel injury, and osteomyelitis. Interventions for exposed mesh after ASC can have significant morbidity (Roth T., Reight I., Laparoscopic mesh explantation and drainage of sacral abscess remote from transvaginal excision of exposed sacral colpopexy mesh, Int Urogynecol J 2012 Jul (7): 953-5). In a large series of 73 patients undergoing mesh excision for extrusions after TVM kit, sacrocolpopexy, and synthetic MUS procedures, the majority of morbidity and adverse events occurred during management of complications following sacrocolpopexy. (Tijdink MM, et al., Surgical management of mesh-related complications after prior pelvic floor reconstructive surgery with mesh, Int Urogynecol J 2011; 22(11):1395-1404).

b. **Infection**

Type 1 mesh (macroporous, monofilament) contains pores larger than 75 microns, the required pore size for admission of macrophages, fibroblasts, blood vessels and collagen fibers into the pores (Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia 1997, 1:15-21). Surgical infection as it relates to implantation of synthetic mesh relies on infiltration and proliferation of bacteria (averaging 1 micron) into and within the pores and interstices of the mesh. If mesh spaces were to be less than 10 microns, bacteria cannot be eliminated since macrophages and neutrophils are too large to enter those spaces. Rapid angiogenesis and fibroplasia also defer colonization/growth of bacteria within the sufficiently wide pores of Type 1 mesh. (Amid 1997).

While Plaintiffs' experts state that mesh should not be placed through the vagina because the vagina cannot be sterilized, vaginal surgery is considered ''clean-contaminated surgery'' because the vagina is naturally colonized with bacteria (Normal flora consists of a variety of microorganisms such as Lactobacilli, anaerobic bacteria, Staphylococcus species, Streptococcus species, Enterococcus faecalis). There are also iterations of the sacrocolpopexy where mesh is attached via a transvaginal approach and the mesh brought transperitoneally and fixed to the sacrum. Despite the potential for low density colonization with potentially pathogenic species (studied in collagen-coated PP mesh) and the inability to sterilize the vaginal field, infection is

uncommon with type 1 macroporous polypropylene mesh (Vollebregt A et al. Int Urogynecol J Pelvic Flo or Dysfunct 2009 20:1345-1351). Infection is usually linked to other types of mesh material implanted and xenografts. Concerns about infection with Prolift and Gynemesh PS, and specifically regarding bacterial colonization of Prolift and Gynemesh PS, are not supported by the medical literature. Infected mesh is not reported as a complication in the RCTs and case series on Prolift.

When infections do occur they can occur with or without vaginal mesh exposure (and whether the mesh is placed transvaginally or abdominally). The treatment of infected abdominal mesh and infectious disease complications of abdominally placed mesh are more morbid than those of vaginally placed mesh. (Roth et al, Laparoscopic mesh explantation and drainage of sacral abscess remote from transvaginal excision of exposed sacral colpopexy mesh, Int Urogynecol J 2012, 23(7):953-955; Tijdink et al, Surgical management of mesh-related complications after prior pelvic floor reconstructive surgery with mesh, Int Urogynecol J, 2011, DOI 10.1007/s00192-011-1476-2.) There are no studies regarding TVM and infection rate in the absence of using prophylactic antibiotics, as administration of a first generation cephalosporin, with or without an additional antibiotic for added anaerobic coverage is commonly practiced.

c. Mesh Shrinkage

All experienced surgeons know that scar tissue can contract, and therefore such contraction is expected. However, contraction of Gynemesh PS mesh and macroporous polypropylene mesh itself has not been demonstrated. Although the term "mesh contracture" is used in some journal articles on Prolift and described as a complication, none defines what that denotes or how it was quantified. Moreover, claims of mesh shrinkage or contraction are typically based on studies using single time points (i.e. not on longitudinal observations on individual patients) and therefore claims of mesh contraction are unreliable. (Letouzey V et al., Ultrasound evaluation of polypropylene mesh contraction at long term after vaginal surgery for cystocele repair, Int Urogynecol J 2009 20:s205-6) (Tunn R et al., Sonomorphological evaluation of polypropylene mesh implants after vaginal mesh repair in women with cystocele or rectocele, Ultrasound Obstet Gynecol 2007 29:449-52) (Velemir L et al., Transvaginal mesh repair of anterior and posterior vaginal wall prolapse: a clinical and ultrasonographic study, Ultrasound Obstet Gynecol 2010 35:474-80).

Contrary to these studies, Dietz et al., found no evidence of mesh contraction in their longitudinal study of 40 women after transobturator PERIGEE mesh implantation. The authors performed four-dimensional ultrasound at 3-53 months at least twice in each to measure mesh dimensions at two time points after implantation (Dietz HP et al. Mesh contraction; myth or

reality? AJOG 2011 204(173) e1-4). Dietz found that mesh length at rest and at valsalva increased by 10% over a period of 18 months on average.

Measures of pre and postoperative vaginal lengths indirectly assess the possibility of mesh shrinkage and none of the RCTs of TVM showed any difference in change in vaginal length between mesh and nonmesh groups.

d. Dyspareunia

Dyspareunia is a potential complication of all prolapse repair surgeries. Studies have not conclusively identified risk factors for postoperative dyspareunia after POP surgery. Overall, the prevalence of dyspareunia postoperatively with traditional prolapse repair ranges between 9 – 47%, and rates of de novo dyspareunia after traditional prolapse repair range from 14.5% to 36.1%. (Maher et al., Surgical management of pelvic organ prolapse in women: a short version Cochrane review. Neurourol Urodyn 2008, 27:3-12; Handa et al., Sexual function before and after sacrocolpopexy for pelvic organ prolapse. Am J Obstet Gynecol 2007;197:629.e1-6; Lowman et al. Does the Prolift system cause dyspareunia? Am J Obstet Gynecol 2008;199:707.e1-6.)

Komesu et al reported that many patients after native tissue posterior repair report the sensation of vaginal "tightness," and they hypothesize that this sensation is related to the 'synergy' between multiple procedures or patient apprehension (Komesu YM et al., Posterior repair and sexual function, AJOG 2007 197:101.e1-6). Helstrom and Nilsson have speculated that the high rate of dyspareunia after traditional POP surgery might be due to decreased elasticity and scarring, impaired nerve function, and reduced blood flow to the vagina. (Helstrom L, Nilsson B., Impact of vaginal surgery on sexuality and quality of life in women with urinary incontinence or genital descensus, Acta Obstet Gynecol Scand 2005 84:79-84.)

The majority of the TVM RCT's have assessed sexual function but not always as the primary outcome measure. In Nieminen's 2008 study, the dyspareunia score was significantly worse in the nonmesh group at 2 years out (Nieminen K, et al., Symptom resolution and sexual function after anterior vaginal wall repair with or without polypropylene mesh, Int Urogynecol J 2008 19:1611-1616). In Miller et al, (Miller D, et al., Prospective Clinical Assessment of the Transvaginal Mesh Technique for Treatment of Pelvic Organ Prolapse—5-Year Results, FMPRS 2011, 17(3) 139-143) a multi-center prospective trial of Prolift, 66/85 women were available for follow-up at 5 years. Only 1 case of de novo dyspareunia was observed in the patients sexually active prior to surgery, whereas in 8 out of 12 with preexisting dyspareunia experienced resolution of dyspareunia with surgery. Similar findings of a net positive effect on sexual function have been observed in other Prolift studies (Milani AL et al. Trocar guided total tension-free vaginal mesh repair of post-hysterectomy vaginal vault prolapse Int Urogynecol J 2009 20(10): 1203-1211) (Hinoul P et al., A Prospective Study to Evaluate the Anatomic and Functional Outcome of a Transobturator Mesh Kit (Prolift Anterior) for

Symptomatic Cystocele Repair, J Min Inv Gynecol 2008 15(5): 615-620). Some studies have shown equivalent sexual function between TVM and nonmesh groups (Withagen et al, Trocar-Guided Mesh Compared With Conventional Vaginal Repair in Recurrent Prolapse, Obstet Gynecol 2011, 117(2:1):242-250) (Sivaslioglu AA, et al, A randomized comparison of polypropylene mesh surgery with site-specific surgery in the treatment of cystocele, Int Urogynecol J 2008 19: 467-471). (Nguyen JN et al., Outcome After Anterior Vaginal Prolapse Repair, Obstet Gynecol 2008: 111(4): 891-898) (Carey M et al., Vaginal repair with mesh versus colporrhaphy for prolapse: a randomised controlled trial, BJOG 2009 116(10): 1380-1386) (Iglesia C et al, Vaginal mesh for prolapse: a randomized controlled trial, Obstet Gynecol 2010, 116(2:1):293-303) (Nieminen K et al, Outcomes after anterior vaginal wall repair with mesh: a randomized, controlled trial with a 3 year follow-up, AJOG 2010: 203(235): e1-e8) (Altman 2011).

Lowman et al, specifically looked at the de novo dyspareunia rate with Prolift. They found a 16.7% rate of de novo dyspareunia after Prolift, which is comparable to that reported with traditional POP repairs. (Weber AM et al., Sexual function and vaginal anatomy in women before and after surgery for pelvic organ prolapse and urinary incontinence, AJOG 2000 182: 1610-5) (Maher CF et al., Abdominal sacral colpopexy or vaginal sacrospinous colpopexy for vaginal vault prolapse: a prospective randomized study, AJOG 2004 190: 20-6) (Higgs P et al., Abdominal sacral colpopexy: an independent prospective long-term follow-up study, NZJOG 2005 45; 430-4) (Holley RL et al., Sexual function after sacrospinous ligament fixation for vaginal vault prolapse, JRM 1996 41: 355-8). However, in the Lowman study, of those women who reported dyspareunia before Prolift, 50% stated that their dyspareunia improved after Prolift (Lowman JK et al. Does the Prolift system cause dyspareunia? AJOG 2008 199: 707.e1-707.e6). Notably, 94.7% of all sexually active women in the study who answered questionnaires answered "true" to the question, "Overall, the Prolift surgery has improved my quality of life and I would have this surgery done again." This satisfaction after Prolift, despite some occurrence of de novo dyspareunia (consistent with de novo dyspareunia rates after other POP repairs), highlights the impact of POP on QOL and indicates that the presence or absence of dyspareunia is not the sole determinant in an individual woman's perception of sexual well-being. 92% of the patients with de novo dyspareunia in Lowman's study described 'insertional dyspareunia' or 'dyspareunia throughout the act of intercourse.' The authors postulated this might be due to levator myalgia. These patients had relief with physical therapy and/or antispasmodic medication or with continued intercourse. Of the 21 patients who had de novo dyspareunia, only 2 had "banding" of the mesh; one required surgical revision because she couldn't tolerate physical therapy, possibly related to having interstitial cystitis; and the other patient's dyspareunia resolved with physical therapy. No other explanations for pain / dyspareunia were elaborated by the report.

In a 7 year retrospective review, Kozal et al examined outcomes using Prolift. Of 64 patients who were sexually active preop (57.1%), de novo dyspareunia occurred in 9 (16.07%), consistent with Lowman et al. (Kozal S et al. Morbidity and functional mid-term outcomes using Prolift pelvic floor repair systems. CUAJ 2014 8 (9-10) e605-9.)

Meyer et al showed that Prolift did not negatively impact sexual function at long-term follow-up based on validated measures, and high rates of patient satisfaction were also documented. (Meyer I et al., Synthetic Graft Augmentation in Vaginal Prolapse Surgery: Long-Term Objective and Subjective Outcomes, JMIG 2016 DOI 10.1016/j.jmig.2016.02.014)

In the review done as part of the Fifth International Collaboration on Incontinence, the authors found that the use of mesh in the anterior compartment is associated with neither a worsening in sexual function nor an increase in de novo dyspareunia compared with NTR (grade B). There was insufficient information to provide meaningful recommendations on sexual function after partially absorbable meshes (grade D). (Dietz V and Maher C., Pelvic organ prolapse and sexual function, Int Urogynecol J 2013 24:1853-1857).

viii. Recall Bias

The phenomena of recall bias reminds us of the importance of objective assessment of patient-reported outcomes of surgery and condition prior to surgery. In Lowman's discussion, the authors raise the concept of 'recall bias' as it related to their assessment of dyspareunia. Recall bias is an issue with the accuracy of the information self-reported by subjects when questioned during a medical study or any investigation. Recall bias arises when there is intentional or unintentional differential recall (and thus reporting) of an outcome by subjects in one group compared to the other (Grimes D, Schulz K. Bias and causal association in observational research. Lancet 2002; 359: 248-252). In Lowman's study, for example, assessing dyspareunia by 2 different methods led to different results. Six patients reported de novo dyspareunia by chart review/telephone interview and 13 reported de novo dyspareunia by questionnaire. The questionnaires were mailed out early in the course of the study (approximately 3 months before final chart review), and 5 patients who reported immediate postop dyspareunia reported that it resolved at the time of chart review.

Recall bias can also inflate patient self-reports of a complication such as de novo dyspareunia after a procedure; for example, patients with pain who are asked to recall whether or not pain was also present prior to surgery may not recall that it was, and may instead associate the surgery with current discomfort. At Lowman's center (and at mine) all patients are asked if they have pain with intercourse on intake questionnaires and at their follow-up visits. Lowman ultimately used chart review which allowed for a more objective comparison of each patient's preop vs postop status.

Related to the issue of "recall bias" is patients' declining ability to remember the risks they were advised of during the informed consent process. McFadden and colleagues found that surgical risk recall declined from 92% immediately post-consent to 72% at only 6 weeks postoperatively. Even recall that mesh was placed during patients' procedure declined from 98% to 84% from immediately post-consent to 6 weeks postop. (McFadden B.L. et al., Patient recall 6 weeks after surgical consent for midurethral sling using mesh, Int Urogynecol J 2013, 24:2099-2104.

ix. Biocompatibility of Polypropylene Mesh

In the case of successful biomaterial implantation, the material induces a transient acute inflammatory response, which leads to constructive remodeling and material integration. Failed implants (of any material) may be subject to mechanical failure or being recognized as 'non-self' and isolated from body tissues and lack of integration. If a biomaterial is cytotoxic, one would expect associated tissue necrosis and no incorporation into surrounding tissue.

Inflammation is an important process not only responsible for clearing a wound of debris and necrotic/abnormal material, but equally crucial for tissue remodeling and regeneration. *We should not assume that inflammation related to a biomaterial implant equates to poor patient / surgical outcomes.* (Brown BN et al., Macrophage polarization: an opportunity for improved outcomes in biomaterials and regenerative medicine, Biomaterials 33(15): 3792-3802.) The transient acute inflammatory response to large pore polypropylene mesh is short-lived and is needed for healing and tissue incorporation. Elmer et al reported an increase in macrophages and mast cell counts and a mild but persistent foreign body response to polypropylene meshes (Elmer C, et al, Histological Inflammatory Response to Transvaginal Polypropylene Mesh for Pelvic Reconstructive Surgery, J Urol 2009, 181(3) 1189–1195).

During development of the TVT—as during development of the Prolift, as noted by Berrocal et al--different materials were trialed: Teflon, Gore-Tex, Mersilene, the majority leading to tape rejection by the patient. Indeed, other kinds of grafts exist and may be used for prolapse repair, including autografts (harvested from the patient), allografts (from human cadavers) and xenografts (from non-human sources such as bovine and porcine grafts). Macroporous monofilament polypropylene has the best evidence of host tissue incorporation/integration, safety and biocompatibility and is the graft material most used mesh in pelvic floor repair. (Amid PK, Classification of biomaterials and their related complications in abdominal wall surgery, Hernia, 1997, 15-21.)

Falconer et al. reported a study on Prolene and Mersilene meshes. Mersilene was found to induce a higher inflammatory response compared to Prolene, which triggered a minimal inflammatory reaction, no tape rejections, and no change in collagen extractability - a marker for increased risk of tape rejection (Falconer C, et al., Influence of Different Sling Materials on Connective Tissue Metabolism in Stress Urinary Incontinent Women, Int Urogynecol J 2001 12(2) S19–S23). There were no histological differences in associated para-urethral connective tissue in biopsies from patients who had Prolene tape implanted (2 years postop) and in controls (continent women who had not undergone a sling).

Pierce et al reported a long-term study comparing biological and synthetic grafts implanted in rabbits. Polypropylene caused a milder inflammatory reaction with more long-term, better host tissue incorporation compared to natural grafts (Pierce LM, et al., Long-term histologic response to synthetic and biologic graft materials implanted in the vagina and abdomen of a rabbit model, AJOG 2009 200(5) 546.el–546.e8).

a. Post-implantation changes/ biomechanics

As noted above, polypropylene implantation creates a wound reaction, followed by granulation tissue with macrophages, giant cells, lymphocytes and polymorphonuclear leukocytes. This reaction is followed by the creation of collagen III, which in some weeks converts to collagen I, which covers the implanted mesh fibers. (Petros PE, Ulmsten UI and Papadimitriou J: The autogenic ligament procedure: a technique for planned formation of an artificial neoligament. Acta Obstet Gynecol Scand Suppl 1990; 153: 43. 16). It has been documented that polypropylene fibers are entirely encapsulated by collagen within 2 weeks of being implanted (Papadimitriou J and Petros P: Histological studies of monofilament and multifilament polypropylene mesh implants demonstrate equivalent penetration of macrophages between fibrils. Hernia 2005; 9: 75) (Petros PE and Richardson PA: Midurethral Tissue Fixation System sling—a 'micromethod' for cure of stress incontinence—preliminary report. Aust N Z J Obstet Gynaecol 2005; 45: 372). This process quarantines and eliminates any bacteria. It has been scientifically demonstrated for up to 24 weeks that polypropylene maintains its morphology and strength after implantation (Spiess PE et al, The tensile properties of tension-free vaginal tape and cadaveric fascia lata in an in vivo rat model, BJU International 2004 93(1) 171–173. Zorn KC, et al., Long-term tensile properties of tension-free vaginal tape, suprapubic arc sling system and urethral sling in an in vivo rat model, J of Uro 2007 177(3) 1195–1198).

b. Toxicity

Polypropylene has not been demonstrated to be toxic. The FDA has specifically validated safe and effective use of polypropylene in the human body over many decades. The assertion that, on implantation, the release of hydrogen peroxide and mediators (if not from bacteria) but from leukocytes/macrophages leads to an oxidative process – which is purported to degrade mesh – has not been observed in the absence of infection or erosion. (Clave A et al., Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants, Int Urogynecol J 21(2010); (Ong KL et al. The myth: in vivo degradation of polypropylene meshes Int Urogyn J 2016 27: s37-8); (Thames S et al., The myth: in vivo degradation of polypropylene-based meshes, Int Urogynecol J, DOI 10.1007/s00192-016-3131-4.).

c. Bacterial slime/Bio-film

No reliable scientific data has demonstrated that, after implantation of Gynemesh PS, bacteria commonly contaminates the mesh and introduces "bacterial slime." Prior work reveals that even with tapes placed in the vagina for 6 to 12 weeks in animals and humans, only "mixed organisms" with scant growth or no growth are cultured. (Petros PE, Ulmsten UI and Papadimitriou J: The autogenic ligament procedure: a technique for planned formation of an artificial neoligament. Acta Obstet Gynecol Scand Suppl 1990; 153: 43. 16) (Petros PE and Ulmsten UI: The combined intravaginal sling and tuck operation. An ambulatory procedure for cure of stress and urge incontinence. Acta Obstet Gynecol Scand Suppl 1990; 153: 53) (Petros PE: Development of the intravaginal slingplasty, and other ambulatory vaginal procedures. Doctoral thesis. Perth: University of Western Australia 1999). The reason for this finding is that bacteria are immediately attacked by leukocytes and macrophages and eliminated (Papadimitriou J and Petros P: Histological studies of monofilament and multifilament polypropylene mesh implants demonstrate equivalent penetration of macrophages between fibrils. Hernia 2005; 9: 75).

d. **Degradation of Polypropylene**

Critics of Prolift and Gynemesh PS state that degraded mesh leads to short-term and long-term complications, but there is no reliable scientific data on which to base these assertions.

Although Clave et al noted that in a minority of explanted polypropylene specimens (various manufacturers) there was evidence of ultrastructural degradation and surface cracking on scanning electron microscopy (SEM) (Clave A et al., Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants, Int Urogynecol J 21(2010) 261-270), all samples were from patients with polypropylene mesh complications (infection and exposure). The authors could not rule out that the effect they were describing was not related to the handling and explantation of the mesh itself. It remains undetermined whether changes noted in the mesh occurred before or after the exposure/infection.

Clavé et al note that, despite exhaustive testing, they could not explain their findings. These authors further noted that they were able to perform chemical analysis in only 32 of 84 explants, which is too small a sample for an appropriately powered study and to draw meaningful conclusions. As Clavé et al stated, "Several hypotheses concerning the degradation of the PP are described. None of these, particularly direct oxidation, could be confirmed in this study."

In two series in which mesh was removed for non-infective reasons, investigators concluded that no graft degradation occurred in the polypropylene mesh material, and that autologous and cadaveric fascia had the most demonstrable graft degradation. (Fletcher SG and Lemack GE:

Re: Histologic comparison of pubovaginal sling graft materials: a comparative study. Urology 2008; 72: 721) (Woodruff AJ, Cole EE, Dmochowski RR et al: Histologic comparison of pubovaginal sling graft materials: a comparative study. Urology 2008; 72: 85)

Ong, White and Thames analyzed the morphology of explanted polypropylene mesh using a novel cleaning process and where there was consideration given to the formalin fixation process. At each intermediate cleaning step, light microscopy, Fourier Transform Infrared Spectroscopy, and SEM was performed. The authors' findings refute the claim that polypropylene oxidized or degraded in vivo, and they demonstrated non-degraded fibers with no damage. A "cracked layer" was composed of adsorbed protein coating, "arising from a well-established phenomenon upon implantation"; adsorbed proteins when placed in formalin "crosslinked and formed a hard, brittle, protective composite layer." (Ong KL et al. The myth: in vivo degradation of polypropylene meshes Int Urogyn J 2016 27: s37-8) The authors thus confirmed the in vivo stability of properly formulated polypropylene. (Thames S et al., The myth: in vivo degradation of polypropylene-based meshes, Int Urogynecol J, DOI 10.1007/s00192-016-3131-4.)

Such purported ultrastructural changes cited by critics of Prolift and Gynemesh PS do not have a realizable impact on patient outcomes based on long-term follow-up of patients implanted with polypropylene midurethral slings (Tommaselli GA et al., Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and meta-analysis, Int Urogynecol J 2015;26 1253-68) (Nilsson CG et al., Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence, Int Urogynecol J 2013; 24 1265-9) and on 7-year follow-up of patients with Prolift (Kozal S et al. Morbidity and functional mid-term outcomes using Prolift pelvic floor repair systems. CUAJ 2014 8 (9-10) e605-9).

e. Carcinogenesis

As recognized by AUGS-SUFU in their publication "Frequently Asked Questions by Patients, Mid-urethral Slings for Stress Urinary Incontinence," dated March 2014, there is no evidence that polypropylene mesh midurethral slings have ever caused cancer or other diseases, despite their widespread use over many years. Tumor formation related to biomaterials in animals is well known to depend more on the physical rather than the chemical configuration of the implant: smooth / large surface areas being carcinogenic and irregular disrupted surfaces / porous surfaces (meshes) lack carcinogenicity (Moalli et al., Polypropylene mesh: evidence for lack of carcinogenicity,Int Urogynecol J March 2014, 25(5): 573-576).

Moreover, King followed 2,361 polypropylene mid-urethral sling patients for up to 122.3 months and no sarcomas were reported (King AB, et al. Is there an association between polypropylene mid-urethral slings and malignancy? Urology 2014; 84:789-92); and in a

study of 2,474 patients followed for a median of 5 years, Linder et al found that although two new cancers with an incidence of 0.08% were diagnosed in the cohort, that rate was not inconsistent with the expected incidence of those cancers in the patient population. (Linder et al, Evaluation of the local carcinogenic potential of mesh used in the treatment of female stress urinary incontinence 2016, DOI 10.1007/s00192-016-2961-4.).

To date, no mesh site cancers have been reported, despite millions of polypropylene midurethral slings having been used since the mid 90's. Nor have any mesh site cancers been reported after implantation of Gynemesh PS or Prolift. We can also extrapolate the safety and biocompatibility of Prolene in that it has been in use as suture and hernia mesh for decades. No reliable scientific data have ever demonstrated an association between use of polypropylene mesh and cancer in humans.

x. What about Vypro, PVDF/Dynamesh and Ultrapro mesh?

Vypro is a mixed fiber mesh composed of half absorbable (polyglactin 910) and half non-absorbable polypropylene fibers. Ultrapro is similarly polypropylene and absorbable poliglecaprone. Ultrapro and Vypro have not been demonstrated to be safer or more efficacious than Gynemesh PS in the POP literature.

One study that analyzed mixed mesh (Vypro vs. polypropylene) to treat POP found an erosion rate of 7% for both meshes; post hoc power analysis indicated the study had low power to detect a difference in mesh exposure rates between mesh types (Achtari et al, Risk factors for mesh erosion after transvaginal surgery using polypropylene (Atrium) or composite polypropylene/polyglactin 910(Vypro II) mesh, Int Urogynecol J 2005 16:389-394). The authors of an abstract presented at ICS/IUGA in 2004 (Denis S et al. Pelvic organ prolapse treatment by the vaginal route using a Vypro composite mesh: preliminary results about 106 cases) concluded that tolerance of the Vypro mesh was very poor.

One RCT randomly assigned 114 patients to standard anterior colporrhaphy with midline plication, ultralateral native tissue colporrhaphy with dissection taken laterally to the limits of the pubic rami, or standard colporrhaphy plus polyglactin mesh graft placement (Vypro) (Weber AM, Walters MD, Piedmonte MR, et al. Anterior colporrhaphy: a randomized trial of three surgical techniques. Am J Obstet Gynecol 2001;185(6): 1299–304 [discussion: 1304–6]). The primary outcome measured was anatomic success. The study found that the addition of Vypro absorbable mesh to traditional repair did not substantially improve anatomic cure rates.

Ultrapro has not been studied for treatment of pelvic organ prolapse to the extent that Gynemesh PS has been; however, where Ultrapro has been studied, it has shown rates of mesh exposure and dyspareunia that are comparable to Gynemesh PS, and it has not been demonstrated to be more

efficacious. (Milani et al., Medium-Term Clinical Outcomes Following Trocar-Guided Mesh Repair of Vaginal Prolapse Using Partially Absorbable Mesh, Int Urogynecol J 2012, 23 (Suppl):S43-S244; Bhatia, N., et al. A Comparison of Sexual Function Outcomes 1 Year After Undergoing a Transvaginal Mesh Procedure Using Polypropylene Mesh vs. Hybrid Polypropylene/Poliglecaprone Mesh. Female Pelvic Med Reconstr Surg March/April 2012; 18(no. 2, supp. 1): S20; Quenemer J et al. Rate of re-interventions after transvaginal pelvic organ prolapse repair using partially absorbable mesh: 20 months medium follow-up outcomes. Eur J Obstet Gynecol Reprod Biol 2014; 175:194-8; Lensen EJM et al., Comparison of two trocar-guided trans-vaginal mesh systems for repair of pelvic organ prolapse: a retrospective cohort study, Int'l Urogynecol. J. (2013))

Likewise, the medical literature does not show that polyvinylidene fluoride (PVDF) or Dynamesh are safer or more effective than Gynemesh PS. PVDF/Dynamesh have not been studied for use in pelvic floor as Prolift/Gynemesh PS have been. Indeed, these materials are not commercially available for use in pelvic floor repairs in the United States.

iii. Prolift Patient Brochure

I have reviewed the Prolift patient brochures, and it is my opinion that the warnings information included in them is appropriate and helpful to patients. The brochures are to be used in conjunction with the surgeons' conversations with their patients regarding treatment options, and the risks and benefits of those options. It is the responsibility of the surgeon to discuss risks and benefits of any surgery offered to his or her patient, including rates of complications of the product seen in his or her own hands. and benefit and risk information that is appropriate to each individual patient given each patient's medical history and condition.

D. IFU and Professional Education Materials

The Prolift and Gynemesh PS IFUs, as well as Ethicon's professional education materials, including the Prolift Surgical Technique Guide, the Prolift Surgeon's Resource Monograph, appropriately warn of the risks of the devices.

The IFU is never assumed to be a completely comprehensive list of every possible adverse complication, such as those that are commonly known to all pelvic surgeons and those that are remote risks. The purpose of the IFU is to provide appropriate risk and benefit information as well as instructions for device use. *The IFU does not replace the informed consent process, clinical judgment, surgical training and experience, and continuing medical education on the part of the surgeon.*

Experienced surgeons are aware of the intraoperative and post-operative risks inherent in the use of surgical mesh. Knowledge of the risks and complications of surgery for pelvic organ prolapse is a fundamental part of our surgical training and education. The risks also have been publicized in the peer-reviewed scientific literature and at professional conferences and meetings, as well as in the 2008 and 2011 FDA public health notifications. As experienced pelvic surgeons know, complications can occur during and after all surgeries performed for POP (ACOG Committee Opinion 513 (2011)/AUA Position statement on the use of vaginal mesh for the repair of POP (2011)). As stated herein, the risks of the Prolift kit and POP repairs using Gynemesh PS are also risks of other surgeries to treat pelvic organ prolapse and are therefore well known to experienced pelvic surgeons.

The risks conveyed in the Prolift and Gynemesh PS IFUs, and in Ethicon's professional education materials, are appropriate because they accurately reflect the risks reported in peer-reviewed medical literature, those observed by experienced pelvic surgeons such as myself and those discussed by my peers at medical conferences.

While I have also considered the FDA's Device Labeling Guidance #G91-1 "Blue Book Memo," 21 CFR 801.109(c) on the labeling of prescription devices, as well as Ethicon's Standard Operating Procedure on Labeling, I consider the most important source supporting the adequacy of the Prolift and Gynemesh PS warnings information to be the peer reviewed medical literature. This is because it is the peer-reviewed literature that provides detailed and scientifically documented information on what adverse events have actually been experienced by women implanted with these devices.

The Prolift Surgeon's Resource Monograph was written by surgeons and compiled the experience of multiple users of Prolift. It provides an in-depth discussion of surgical technique for implanting Prolift and of intra-operative complications including hemorrhage, visceral injury and ureteral obstruction and postoperative complications including dyspareunia, vaginal pain, erosions and exposure, hemorrhage, hematoma, fistula, infection, and urinary retention. The 2007 Prolift professional education slide deck includes discussion of complications including injury to adjacent organs, bleeding, hemorrhage, cellulitis, abscess, hematoma, contraction, de novo SUI, fistula, mesh exposures, dyspareunia and pain.

E. Prolift+M

i. Mechanical Properties of Prolift+M Partially Absorbable Mesh

The mesh in Prolift+M is a 50-50 blend of poliglecaprone-25 knitted with polypropylene. After three months, the poliglecaprone-25 (Monocryl) is absorbed, decreasing the weight of the Prolift+M from 57 g/m^2 to 31 g/m^2 (vs. 45 g/m^2 for Prolift), thereby leaving a lower burden of mesh in situ. The Prolift+M pore size increases from 2.5 to 3.5 mm after absorption Prolift+M provides increased elasticity in the longitudinal direction, secondary to the warp-knitting incorporation of the absorbable poliglecaprone-25, and larger pores allows for more tissue ingrowth. (Lensen, E.J.M., Withagen, M.I.J., Kluivers, K.B. et al., Comparison of two trocar-guided trans-vaginal mesh systems for repair of pelvic organ prolapse: a retrospective cohort study, Int Urogynecol J (2013) 24: 1723).

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Lower mesh density may lead to a more favorable biologic compatibility, i.e., less foreign body reaction. A lower mesh density/burden may also lead to less stress transmission at the tissue-implant interface (Dietz HP, Vancaillie P, Svehla M, Walsh W, Steensma AB, Vancaillie TG (2003) Mechanical properties of urogynecologic implant materials. Int Urogynecol J Pelvic Floor Dysfunct 14:239– 243). The concept is that the transmission of loads at this interface, i.e. stress shielding, may influence the occurrence of complications, such as exposures or de novo prolapse in another compartment. (Jones KA, Feola A, Meyn L, Abramowitch SD, Moalli PA (2009) Tensile properties of commonly used prolapse meshes. Int Urogynecol J Pelvic Floor Dysfunct 20(7):847–853).

Risk factors for mesh exposure have not been completely elucidated and are thought to be multi-factorial as previously reviewed. It is hypothesized that exposure rates are correlated to mesh weight and to the amount implanted or 'mesh burden' (Dwyer PL (2006) Evolution of biological and synthetic grafts in reconstructive pelvic surgery. Int Urogynecol J Pelvic Floor Dysfunct 17(Suppl 1): S10–S15). In the inguinal hernia literature, the superiority of a lightweight mesh compared to a heavier weight mesh with regard to long-term complications and increased comfort has been documented. (Klosterhalfen B, Junge K, Klinge U. The lightweight and large porous mesh concept for hernia repair. Expert Rev Med Devices 2005;2:103-117). However, the hernia 'space' is not the vaginal 'space'. It has been theorized that a lightweight (partially absorbable) vaginal mesh might fulfill these characteristics – but the data are limited.

Existing data on partially absorbable mesh in the vaginal space are comparable to nonabsorbable mesh. Both Prolift and Prolift+M have been demonstrated to be safe and effective.

ii. Safety and Efficacy of Prolift+M

The scientific literature has demonstrated the safety and efficacy of Prolift+M. Despite the theoretical advantages of partially absorbable mesh, the data has shown that the safety and

efficacy of Prolift+M and Prolift are equivalent. My results with Prolift+M are consistent with the results reported in the literature.

In a single-center study, Khandwala examined a prospective cohort of 157 subjects undergoing Prolift+M with a mean follow-up of 13 months. Results included both improvement in function and anatomy at 1 year and low rates of complications. Composite success score was 88.1%. Pure anatomic success based on a resulting POP-Q lower than stage II was 94%. There were 3 cases (2.2%) of mesh exposure. The incidence of de novo dyspareunia was 6%. He found no cases of clinical mesh retraction nor diminution in total vaginal length (from preop to 12 months post op) in the study. He observed no change in anatomic success in follow-up (Khandwala S. Female Pelvic Med Reconstr Surg 2013;19: 84-89).

Similarly, Milani et al was a cohort study (but multi-centered) with a 1 year follow-up (Milani AL, Hinoul P, Gauld JM, et al. Trocar-guided mesh repair of vaginal prolapse using partially absorbable mesh: 1-year outcomes. Am J Obstet Gynecol 2011;204:74, e1-e8) reporting ssignificant improvement in bother, quality of life, and sexual function at 3 months and 1 year compared with baseline. At one year after surgery, 86.2% of patients indicated their prolapse situation to be "much better." Anatomic success, defined as prolapse stage ≤ 1 in the treated vaginal compartments, was 77.4% (95% confidence interval,69.0–84.4%).

Milani et al, also reported only a 2% rate of dyspareunia and 10% rate of mesh exposure. Milani observed a slight decrease in anatomic success over time (limited by the follow-up of 12 months) and reported a low (1.6%) subjectively measured incidence of mesh stiffness at 1 year with Prolift+M. This may be due to the intrinsic properties of the Prolift+M absorbable hybrid system. (Cobb WS, Burns JM, Peindl RD, et al. Textile analysis of heavy weight, mid-weight, and light weight polypropylene mesh in a porcine ventral hernia model. J Surg Res 2006;136:1-7). The low incidence of dyspareunia in Milani et al, as well as Khandwala could be due to the properties of the blended poliglicaprone-25—polypropylene system and the warp knitting that allows increased unidirectional elasticity and reduced fibrotic reaction, which may benefit vaginal distention during intercourse. Limitations of both Khandwala and Milani et al, include the nature of cohort studies (the potential for selection bias and the lack of an appropriate control) and the short (12 month) follow- up.

A retrospective study of 269 patients with a median follow-up of 20 months determined that Prolift+M is efficient and reliable with relatively low rates of re-intervention. The study further showed a low global rate of operative re-intervention after Prolift+M of 8%. Re-intervention for prolapse recurrence was 1.2% and for mesh exposure was 2%. (J. Quemener et al., Rate of re-interventions after transvaginal pelvic organ prolapse repair using partially absorbable mesh: 20 months median follow-up outcomes, European Journal of Obstetrics Gynecology and Reproductive Biology 175 (2014) 194–198). Conclusions drawn from utilizing their historical retrospective comparison group of non-absorbable Prolift may not reflect those from a larger RCT. The study concluded that a partially absorbable mesh does not seem to have advantages when compared with classic non-absorbable mesh regarding rates of re-intervention.

Another retrospective cohort study, by Lensen and colleagues and involving 569 women undergoing either Prolift or Prolift+M, found failure rates to be similar in the two groups

(composite outcome failure (8 % versus 4 %,, p=0.07). (Lensen, E.J.M., Withagen, M.I.J., Kluivers, K.B. et al., Comparison of two trocar-guided trans-vaginal mesh systems for repair of pelvic organ prolapse: a retrospective cohort study, Int Urogynecol J (2013) 24: 1723.) The re-operation rate in the untreated compartments was higher in the non-absorbable mesh group compared with the partially absorbable mesh group (5% vs 1 %), and mesh exposure rate in the non-absorbable mesh group was 12% and in the partially absorbable mesh group it was 5%. However, no clinically relevant difference was demonstrated between the two groups, despite the significant sample size. Other complication and patient satisfaction rates were similar. Both the Quenemer and Lensen studies were limited by a 20 month follow-up.

A drawback of many of the Prolift+M studies is a potential bias, originating from the fact that the two devices were not used simultaneously (Prolift was marketed first), or that Prolift+M was not studied against an appropriate control or that a superiority study was not performed. Some purported superiority data for Prolift+M , particularly later outcomes, may be the result of surgeons' increased experience in performing mesh repairs by the time Prolift+M was marketed. (In that regard, I am not aware of data that compares outcomes of Prolift performed around the time of the 2011 FDA Safety Update versus earlier Prolift surgeries with the same surgeon).

Bhati and colleagues conducted a retrospective cohort study to assess sexual health of patients with Prolift and Prolift+M, as measured by the PISQ-12 (Pelvic Organ Prolapse Urinary Incontinence Sexual Questionnaire). They assessed 39 Prolift patients and 32 Prolift+M patients at four months and 20 patients in each group at one year. They found that PISQ scores were improved significantly in both groups at both four months and one year. Total PISQ scores increased significantly in both groups between four months and one year postoperatively. Although there was higher improvement in postoperative sexual desire, comfort with intercourse and overall sexual function in the Prolift+M group at four months postoperatively, this difference was not found at one year.

Meta-analyses of the scientific literature have demonstrated superior efficacy as well as equivalent safety of transvaginal mesh prolapse repairs utilizing Prolift and Prolift+M as compared to native tissue repairs. (Sun et al, The treatment of anterior vaginal wall prolapse by repair with mesh versus colporrhaphy, Int Urol Nephrol (2016), 48:155–167; Maher C, Feiner B, Baessler K, Christmann-Schmid C, Haya N, Marjoribanks J, Transvaginal mesh or grafts compared with native tissue repair for vaginal prolapse, Cochrane Database of Systematic Reviews 2016, Issue 2; Min et al, Arch Gynecol Obstet (2013) 287:919–936, Meta-analysis of the efficacy and safety of the application of adjuvant material in the repair of anterior vaginal wall prolapse; Haya et al, Polypropylene Mesh for Pelvic Organ Prolapse Surgery, Curr Obstet Gynecol Rep (2013) 2:129–138.) Rates of de novo dyspareunia, pelvic pain and genital pain after both Prolift and Prolift+M are low and sexual function and total vaginal length (after both Prolift and Prolift+M) are similar to those after native tissue repair.

iii. Prolift+M Patient Brochure

I have reviewed the Prolift+M patient brochure, which may be provided by surgeons to patients considering Prolift+M. The brochure discusses risks including injury to blood vessels or nerves, difficulty urinating, pain, scarring, pain with intercourse, bladder and bowel injury, mesh

exposure and need for mesh removal. They further state that patients should discuss the benefits and risks of the permanent mesh implant with their doctors.

It is my opinion that the warnings information included in the Prolift+M patient brochure is appropriate and helpful to patients. The brochure is to be used in conjunction with the surgeons' conversations with their patients regarding treatment options, and the risks and benefits of those options. It is the responsibility of the surgeon to discuss risks and benefits of any surgery with his or her patient, including rates of complications of the product seen in his or her own practice and benefit and risk information that is appropriate to each individual patient given each patient's medical history and condition.

iv. Prolift+M IFU

The Prolift+M IFU is provided to surgeons in the packaging of every Prolift+M device and provides information as to indications, contraindications, warnings, precautions, adverse reactions and the surgical procedure.

The Prolift+M IFU states that adverse reactions include hematoma, urinary incontinence, urinary retention/obstruction, ureter obstruction, voiding dysfunction, pain, infection potentiation, wound dehiscence, nerve damage, recurrent prolapse, inflammation, adhesion formation, fistula formation, contracture, scarring, mesh exposure, erosion and extrusion, pain with intercourse and pelvic pain that may resolve with time, impairment of normal voiding for a variable length of time, and punctures or lacerations of vessels, nerves, bladder, urethra or bowel. It is my opinion that the Prolift+M IFU appropriately warns surgeons of the risks of Prolift+M.

The list of risks enumerated in the Prolift+M is not exhaustive and surgeons do not need it to be. The risks of pelvic surgery, including but not limited to those listed in the IFU for Prolift+M, are commonly known to pelvic surgeons. The IFU is not intended to teach pelvic surgery to users. Surgeons are trained in pelvic surgery in medical school, residency, fellowship, in professional education and continuing medical education courses. They know the risks of pelvic surgery from this training as well as from their personal experience, reading the medical literature, discussions with peers, participation in professional scientific conferences, professional education courses and literature (including the Prolift Surgical Technique Guide and the Surgeon's Resource Monograph), and the FDA's 2008 and 2011 public health notices.

I have reviewed IFUs for numerous medical devices, including other meshes for pelvic floor repair. The IFU is consistent with IFUs for other medical devices.

I am not a regulatory expert, but I have reviewed the FDA's Blue Book Memo, Device Labeling Guidance #G91-1, and 21 C.F.R. 801.109(c), which provide that relevant hazards, contraindications, side effects and precautions may be omitted from the medical device packaging if they are commonly known to practitioners licensed by law to use the device. All of

the risks of Prolift+M surgery, including those in the Prolift+M IFU, are well known to pelvic surgeons.

v. Biocompatibility of the Mesh in Prolift+M

As discussed earlier in my report, although plaintiffs' experts have questioned the biocompatibility of polypropylene mesh, polypropylene has been used in the human body for decades. My opinions as to the biocompatibility of the mesh in Prolift apply equally to the mesh in Prolift+M and are supported by the scientific literature on Prolift and Prolift+M cited herein. There is no clinical evidence that the mesh in Prolift+M is cytotoxic or that it degrades. There is no peer-reviewed scientific literature that supports the theory that the mesh in Prolift+M is cytotoxic or that it degrades. I also have never seen evidence in my practice that the mesh in Prolift+M is cytotoxic or that it degrades. I have never seen any inappropriate inflammatory response to Prolift+M in my patients, and the peer-reviewed scientific literature supports my observations. Finally, I have never seen cancer develop in any of my patients as a result of implantation with Prolift+M, and there is no peer-reviewed scientific literature supporting an association between Prolift+M implantation and malignancy.